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Snakebite Envenoming: A Public Health Perspective

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1. Introduction

Envenomings by snakebites constitute a highly relevant public health problem on a world wide basis, particularly in tropical regions of Africa, Asia and Latin America (Gutiérrez et al., 2006; WHO, 2007a). It affects mostly agricultural workers and their children living in rural settings. Thus, its highest impact occurs in poor and politically underpowered people, thus representing a 'disease of poverty' (Harrison et al., 2009) which fulfils the characteristics of a truly neglected tropical disease. Accordingly, the World Health Organization (WHO) incorporated, in 2009, snakebite envenoming in its list of neglected tropical diseases (www.who.int/neglected_disease/diseases/en). Despite the high impact of this pathology in terms of morbidity and mortality in vast regions of the world, it has received little attention from international health agencies and foundations, research agendas, and pharmaceutical companies, even when compared with other neglected diseases which have received a well deserved growing attention over the last decade (Williams et al., 2010). Such low concern for an important disease is due in part to the lack of political voice of the groups affected by snakebites, to the weakening of public health systems in many developing countries, and to the poor documentation of the actual global impact of this problem, which makes the advocacy to confront this neglected disease a difficult task. The present chapter reviews the main features associated with snakebite envenoming and its treatment, and highlights some of the most pressing tasks that need to be undertaken to confront this public health problem.

2. Assessing the actual impact of snakebite envenoming

The actual incidence and mortality associated with snakebite envenoming is poorly known, in part due to the lack of reliable information on this disease in many regions of the world. Although health statistics, based on the reports of hospital cases to health authorities, are satisfactory in some countries (for example in Brazil, de Oliveira et al., 2009), for many countries and regions this information is largely deficitary (Gutiérrez et al., 2010b; WHO, 2007a). This is in part due to the fact that health statistics are poor in many countries, and also that many people affected by snakebites do not seek medical attention and instead rely on local traditional healers, thus remaining invisible to health authorities (Habib et al., 2001; Michael et al., 2010; Otero et al., 2000; Sharma et al., 2004). Despite these limitations, a

number of studies have generated valuable information on the real impact of snakebite envenoming. Snakebites affect mainly agricultural workers and their relatives, living in poor rural settings of Africa, Asia and Latin America (Alirol et al., 2010; Chippaux, 2010; Fan & Cardoso, 1995; Warrell, 2010). Thus, it is clearly an occupational hazard. Incidence is usually higher in men than women, and children are also affected mostly due to their involvement in agricultural duties. Most bites occur in lower limbs, although bites in hands are also frequent (Alirol et al., 2010; Warrell, 2010). Incidence varies along the year, associated with the rainy season and with the timing of agricultural activities (Chippaux, 2010). Natural disasters have been associated with increments in the number of snakebites, as shown in Bangladesh during the 2007 monsoon flood (Alirol et al., 2010). Some social and ethnic groups are affected to a higher extent by snakebites, as compared with other groups. In Latin America, for instance, indigenous groups present a high incidence of snakebites (Larrick et al., 1978; Pierini et al., 1996). In addition, these groups are generally more vulnerable owing to their limited access to health services, evidencing a pattern of inequity that has implications in terms of mortality and morbidity secondary to snakebite envenomings (Gutiérrez, 2011). Moreover, these accidents fuel a vicious circle of poverty, since they have a negative impact on the working performance of agricultural workers, thus affecting the already precarious source of income for their families. Thus, in addition of being a disease of the poor (Harrison et al., 2009), snakebites worsens the economic situation of victims and their families.

A pioneer study on mortality due to this pathology was conducted by Swaroop & Grab (1954) on the basis of hospital statistics. Chippaux (1998) estimated an annual total of 5,400,000 bites, over 2,500,000 envenomings and 125,000 deaths due to snakebites. A more recent study by Kasturiratne et al. (2008) estimated a global total of envenomings ranging from 421,000 to 1,841,000, with fatalities ranging from 20,000 to 94,000. These studies presented estimations of envenomings and fatalities by regions as well. South and Southeast Asia present the highest incidence of snakebites, followed by sub-Saharan Africa (Kasturiratne et al., 2008). Likewise, these three regions have the highest numbers of fatalities. However, these estimates were based on the extrapolation of data from some regions and countries and, therefore, have limitations. When community-based surveys have been performed, the picture that emerges is one of a much higher dimension, both in terms of incidence and mortality (Snow et al., 1994; Sharma et al., 2004; Trape et al., 2001). The incidence of snakebites in specific areas can be very high. Examples are the Benue valley of Nigeria (497 per 100,000 population per year, Pugh & Theakston, 1980) and in southeastern Nepal (1,162 per 100,000 population per year, Sharma et al., 2004). A meta-analysis of snakebites in Africa suggested that the actual incidence might be 3-5 times higher than that derived from hospital statistics (Chippaux, 2011). Two recent studies further illustrate this concept. A community-based survey performed in rural Bangladesh revealed an incidence of 623.4 cases per 100,000 population per year (Rahman et al., 2010), which is much higher than the incidence derived from hospital-based statistics. Moreover, a recent study on mortality in India, which was part of a large national representative mortality survey, indicates that there are 45,900 deaths due to snakebite envenoming per year in this country (Mohapatra et al., 2011). The issue of underreporting needs to be addressed by different approaches, such as by identifying regions where underreport is more likely to occur (Hansson et al., 2010), and by performing community-based surveys in countries of high incidence of snakebites.

2.1 Beyond mortality: The impact of sequelae from snakebite envenomings

Case fatality rate in snakebite envenomings, if not properly treated, can be very high, especially in bites inflicted by highly venomous species (Sharma et al., 2004; Warrell, 2010). In addition, a percentage of people that survive develop sequelae as a consequence of envenoming. In the case of bites by viperid snakes, and by some elapids (genus *Naja*) that induce local tissue necrosis, sequelae include tissue loss and dysfunction, which may lead to amputation (S.B. Abubakar et al., 2010a; Gutiérrez & Lomonte, 2009; Otero et al., 2002; Warrell, 2010). Despite the scarcity of statistics on the incidence of sequelae following snakebite, observations in sub-Saharan Africa indicate that up to 20% of the patients, perhaps more, develop permanent physical sequelae (Pugh et al., 1980; Snow et al., 1994). Bites in the hands by viperid species are more prone to leave permanent tissue damage than bites in the lower limbs (Dart et al., 1992). Moreover, people suffering snakebites also present psychological sequelae, as clearly revealed by a recent study in Sri Lanka (S.S. Williams et al., 2011). The combination of physical and psychological consequences of snakebites has a dramatic impact on the quality of life of both patients and dependants. These are mostly poor agricultural workers whose survival depends very much on their physical and emotional stability to confront everyday hardships. In many cases, a large group of people depend on them as the only source of income. Therefore, when snakebite envenomings are analyzed using the parameter of DALYs ('disability adjusted life years') lost, the actual impact of this disease becomes more evident. It is necessary to investigate the effects of this pathology from such broader perspective, through interdisciplinary research projects involving international partnerships and networks.

In order to have a more rigorous and realistic assessment of the actual dimension of snakebite envenoming worldwide, the following tasks should be implemented: (a) Introducing compulsory notification of these envenomings. (b) Implementing the use in death certification of the specific classifier T 63.0 snake venom listed in the International Statistical Classification of Diseases and Related Health Problems (WHO, 2007b). (c) Performing well-designed epidemiological research based on health statistics and community-based surveys. (d) Supporting the training of health staff for proper record keeping on snakebite envenoming in many countries. These and related efforts will contribute to the generation of a solid body of information which will help to raise awareness on the seriousness of this problem and, at the same time, will provide decision-makers with more accurate data for the design of interventions of various sorts (Gutiérrez et al., 2010b).

3. Snake species responsible for the highest toll of envenomings

Snakes capable of inducing serious envenoming in humans are classified in the families Colubridae (*sensu lato*), Atractaspididae, Elapidae and Viperidae. These families include more than 2,600 species, although a relatively reduced number of them, mostly belonging to the families Elapidae and Viperidae, are responsible for the vast majority of snakebite envenomings worldwide (Warrell, 2010). In Asia, the most relevant species belong to the elapid genera *Bungarus* (kraits) and *Naja* (cobras) (Figure 1A), and to various species of the viperid genera *Echis*, *Daboia*, *Trimeresurus* and *Hypnale* (Warrell, 1995a). In Africa, species of *Naja* and few viperids are important in the northern countries, whereas the saw-scale viper

(*Echis ocellatus*) (Figure 1B) inflicts a heavy toll in the sub-Saharan region, together with other viperids classified in the genera *Echis* and *Bitis*, and some cobras (*Naja* sp) (WHO, 2010b). In the Americas, species of rattlesnakes (*Crotalus*) are important in North America, whereas lance-head vipers of the genus *Bothrops*, such as *B. asper* (Figure 1C) and *B. atrox*, are responsible for most snakebites in Central and South America, in addition to a number of *Bothrops* species in South America (Fan & Cardoso, 1995; Gómez & Dart, 1995; Gutiérrez, 2010).

Fig. 1A. *Naja naja* from Sri Lanka. Photo: Mark O'Shea. Reprinted from *Journal of Proteomics* 74, 1735-1767, Williams et al., copyright 2011, with permission from Elsevier.

Fig. 1B. *Echis ocellatus* from Togo. Photo: David Williams. Reprinted from *Journal of Proteomics* 74, 1735-1767, Williams et al., copyright 2011, with permission from Elsevier.

Fig. 1C. *Bothrops asper* from Costa Rica. Photo: Mahmood Sasa. From Gutiérrez et al. (2006) *PLoS Medicine* 3: e150.

In addition, some species, albeit not causing high numbers of bites, are capable of inflicting severe envenomings, such as *Lachesis* sp (bushmaster) and *Micrurus* sp (coral snakes) in the Americas (Warrell, 2004), *Atractaspis* sp (borrowing snakes) and *Dendroaspis* sp (mambas) in Africa/Middle East (WHO, 2010b), and a variety of elapid species in Australia and Papua New Guinea (White, 2010). Envenomings by colubrid species are usually not severe although fatal cases by species of the African genera *Dispholidus* and *Thelotornis* have been described (Warrell, 1995b). The taxonomy of venomous snakes is a highly dynamic field and recent modifications have been introduced in medically-relevant snake taxa (Quijada-Mascareñas & Wüster, 2010). Toxinologists, clinicians and antivenom manufacturers should be aware of these changes in taxonomy. Detailed information on the country distribution of the most important poisonous snakes is available at the WHO website http://apps.who.int/bloodproducts/snakeantivenoms/database/

4. Snake venom biochemistry and toxicology

These groups of 'advanced' snakes have acquired, through a long and complex evolutionary history (Fry et al., 2006, 2009), the ability to synthesize a toxic secretion, i.e. venom, by an exocrine gland located in the maxillary region, together with a venom delivery system based on the presence of ducts and fangs (Meier & Stocker, 1995; Vonk et al., 2008). The molecular evolution of venom toxins has involved an accelerated Darwinian process, by which genes have been duplicated and recruited in venom glands, with a concomitant process of acquisition of toxic functions based on a trend to generate mutations in sequences coding predominantly for amino acid residues located in the surface of these proteins, as well as other molecular mechanisms such as domain loss and neofunctionalization, thus generating a wide versatility in their ability to interact with diverse tissue targets (Casewell et al., 2011; Fry et al., 2006; Kini & Chan, 1999; Ohno et al., 2003). In the last decade, the use of proteomic

tools based on mass spectrometric analysis and sequence determination has allowed a detailed knowledge on the composition of venoms from many species (Calvete et al., 2007; Calvete, 2010; Fox & Serrano, 2008). Understanding the snake venom proteomes ('venomes') provides valuable information for the search of novel toxins and for the design of the most appropriate mixtures of venoms for animal immunization for antivenom production, among other applications (Calvete, 2010; Gutiérrez et al., 2009a).

Venoms from snakes of the family Elapidae comprise a high percentage of proteins of the so-called 'three finger toxin' family, which are low molecular mass (6-9 kDa) polypeptides that exert a number of actions, such as the ability to block neuromuscular junctions at the post-synaptic level by binding with very high affinity to the nicotinic cholinergic receptor of the motor end-plate in skeletal muscle fibers (Hegde et al., 2010). Some three-finger toxins are membrane-disorganizing proteins, named 'cardiotoxins' or 'cytotoxins', which disrupt the integrity of cell membranes and are likely to play a role in the tissue damage associated with envenoming by some cobras (Dufton & Hider, 1988). The venoms of *Dendroaspis* sp (mambas) contain other types of neurotoxins, i.e. dendrotoxins and fasciculins, which interfere with neuromuscular junctions by various mechanisms (Harvey, 2001, 2010). Elapid venoms are also characterized by the high abundance of phospholipases A_2 (PLA_2s), some of which are potent neurotoxins whose mechanism of action relies in the specific binding to receptors in the presynaptic nerve terminal, followed by degradation of phospholipids at the plasma membrane of these terminals, thus affecting the normal process of neurotransmitter release (Rossetto et al., 2006). Other PLA_2s induce acute muscle damage which, in the case of some sea snakes and other elapids, results in systemic myotoxicity, i.e. rhabdomyolisis, associated with myoglobinuria, hyperkalemia and acute renal failure (Gutiérrez & Ownby, 2003). Besides the predominant three-finger toxins and PLA_2s, elapid venoms also contain other proteins in low concentrations, such as cysteine-rich secretory proteins (CRISPs), cobra venom factor and other hydrolases (serine proteinases, metalloproteinases, nucleotidases) (Correa-Neto et al., 2011; Kulkeaw et al., 2007; Petras et al., 2011). The clotting disturbances induced by some Australian elapid venoms are caused by procoagulant serine proteinases which are prothrombin activators (St Pierre et al., 2005)

Venoms of snakes of the family Viperidae present large variations in their composition, but nevertheless the components showing the highest concentrations correspond to zinc-dependent metalloproteinases, PLA_2s and serine proteinases (Calvete, 2010; Fox & Serrano, 2005). In addition, these venoms contain bradykinin-potentiating peptides (BPPs), disintegrins, C-type lectin-like proteins, L-amino acid oxidase and various other enzymes (Calvete et al., 2009). Metalloproteinases are largely responsible for degradation of the basement membrane of microvessels, with the consequent hemorrhage (Escalante et al., 2011), activation of prothrombin and factor X (Kini, 2005; Tans & Rosing, 2001), thus generating the formation of microthrombi and fibrinogen depletion, i.e. defibrinogenation (Gutiérrez et al., 2010a), and degradation of the extracellular matrix (Moura-da-Silva et al., 2009), among other effects. In turn, some viperid PLA_2s induce acute muscle damage at the site of venom injection (Gutiérrez & Ownby, 2003; Lomonte et al., 2003). Some viperid PLA_2s also exert presynaptic neurotoxicity, such as the complex 'crotoxin', abundant in the venom of South American rattlesnakes (Bon, 1997). Serine proteinases are responsible for clotting disturbances, i.e. defibrinogenation, and hypotension (Serrano & Maroun, 2005). Venoms from species of the family Atractaspididae (burrowing asps) contain sarafotoxins, which are low molecular mass components that induce vasospasm leading to cardiac toxicity (Bdolah,

2010). Finally, the venoms of snakes of the polyphyletic family Colubridae have been studied to a lesser extent, but they also contain metalloproteinases, serine proteinases, PLA_2s, CRISPs and neurotoxins (Mackessy, 2002). Snake venoms present a high variability, not only between species, but also between different populations of the same species (Alape-Girón et al., 2008; Chippaux et al., 1991; Jayanthi and Gowda, 1988). Moreover, some species present a conspicuous ontogenetic variability in the composition of their venoms, such as the Central American rattlesnake *Crotalus simus* (Calvete et al., 2010a) and the lance-head viper *Bothrops asper* (Alape-Girón et al., 2008). This high variability in venom composition has evident implications for the clinical manifestations of envenoming (Warrell, 1997) and for the preparation of antivenoms (Gutiérrez et al., 2009a).

5. Clinical manifestations of envenoming

The large variation occurring in venom composition urges caution when classifying the clinical manifestations of snakebite envenoming, since important differences have been described in the clinical features in envenomings by closely-related species or even within a single species. However, there are general trends in the clinical picture of envenoming by the various groups of poisonous snakes. Envenomings by elapid species (sea snakes, tiger snakes and taipans in Australia, cobras and kraits in Asia, cobras and mambas in Africa, and coral snakes in the Americas) are usually characterized by progressive descending neurotoxic paralysis secondary to the action of pre- or post-synaptic neurotoxins at the neuromuscular junctions (Warrell, 1996, 2010; White, 2010). The most serious consequence of this effect is respiratory paralysis, which may lead to death if not properly and timely attended. In addition, envenomings by a number of elapid species are also characterized by rhabdomyolysis, which may lead to acute renal failure (Warrell, 1996). Patients envenomed by elapids in Australia and Papua New Guinea develop coagulation disturbances which may provoke bleeding (White, 2010). On the other hand, human envenomings by some cobras in Asia and Africa are not characterized by neurotoxic manifestations, but instead by local tissue necrosis (Warrell, 1995a, 1995b).

Viperid snake venoms provoke complex and often drastic local pathological effects, i.e. hemorrhage, dermonecrosis, blistering, myonecrosis and edema, always associated with pain (Gutiérrez & Lomonte, 2009; Warrell, 2004). These local manifestations may lead to permanent sequelae, such as tissue loss and dysfunction (Dart et al., 1992; Otero et al., 2002). After systemic venom distribution, and depending on the severity of the case, viperid snakebite envenomings are characterized by coagulopathies, bleeding, renal alterations and hemodynamic manifestations which may lead to cardiovascular shock and multisystem organ failure (Gutiérrez et al., 2009b; Warrell, 2004). Intravascular hemolysis might also occur, in some cases associated with microthrombi formation (Warrell, 1996). Exceptions to this general trend are envenomings by the South American and some populations of North American rattlesnakes, as well as some viperids in the Old World, which induce neurotoxicity (Azevedo-Marques et al., 2009; Ferquel et al., 2007). Despite the existence of these general trends, clinical studies highlight the complexity of snakebite envenoming, as demonstrated by the description of 'unusual' manifestations in cases by some elapids in Asia and South America (Faiz et al., 2010; Manock et al., 2008; Trinh et al., 2010). In addition, some venoms induce unique clinical features, such as the thrombotic effect described for the Caribbean viperid species *Bothrops lanceolatus* and *B. caribbaeus* (Thomas et al., 1996), and the acute hemorrhagic infarction of the pituitary in envenoming by *Daboia russelli* (Tun-Pe et al., 1987).

The severity of snakebite envenoming depends on a number of factors, such as the volume of venom injected, the size and physiological condition of the victim, and the region of the body where venom is delivered. A percentage of snakebites are not associated with venom injection ('dry bites') and, therefore, no clinical manifestations develop (Warrell, 2004). In general, bites in the head tend to be more severe than bites in the extremities, and envenoming in children are more prone to become severe. In the case of envenoming by pit vipers, bites in the hands are more likely to generate sequelae than bites in the lower limbs (Dart et al., 1992). Thus, a proper assessment of the clinical manifestations and severity of snakebites is a key element for the correct diagnosis and clinical management of these accidents.

6. Diagnosis and treatment of snakebite envenomings

6.1 Diagnosis

Identification of the offending snake is often difficult because in many settings there are various similar species and the bitten person is usually unable to differentiate between them. Even when the snake is killed and brought to the health facility, identification is not always correct. In Australia, kits have been developed for the immunodetection of venom in the bite site or in urine, thus allowing the identification of the offending snake (White, 2010). However, this is not the case in the vast majority of regions in the rest of the world. A 'syndromic approach' has been promoted for the diagnosis of the type of envenoming in various parts of the world (Ariaratnam et al., 2009; WHO, 2010b). For instance, in Central America, there are two predominant syndromes in snakebite envenomings: one presenting local pathological effects (swelling, pain, local tissue damage), clotting disturbances and bleeding, and another characterized by descending neuromuscular paralysis. The first syndrome is associated with envenomings inflicted by viperid species, whereas the second is due to envenomings by elapid species (*Micrurus* sp). This clinically-based diagnosis allows for the selection of the correct antivenom, i.e. polyvalent antivenom or anti-coral antivenom, respectively (Gutiérrez, 2010). Such syndromic approach has been advocated in other regions of the world as well, such as in sub-Saharan Africa (WHO, 2010b) and Sri Lanka (Ariaratnam et al., 2009). In large regions of the savannahs in sub-Saharan Africa, cases presenting clotting disturbances are associated with envenomings inflicted by the saw-scale viper, *Echis ocellatus* (Warrell, 1995b). In this context, a simple laboratory test known as the '20 minute whole blood clotting test' represents a useful diagnostic tool (Warrell et al., 1974). In contrast, envenomings associated with a predominantly neurotoxic picture are caused by species of neurotoxic cobras (*Naja* sp) or mambas (*Dendroaspis* sp), and envenomings characterized by local tissue damage without coagulant disturbances are induced by species of *Bitis* or by cytotoxic cobras (WHO, 2010b).

6.2 First aid in snakebite envenoming

Snakebite cases in many regions of the world are initially attended by local healers who use a wide variety of interventions, most of which are ineffective and often exert harmful effects. Examples are the use of ligatures, incisions and suction, cryotherapy, electroshock, and the administration of synthetic or natural substances (Hardy, 2009; Warrell, 2010). Other interventions, such as application of 'black stone' or suction devices are largely ineffective for the removal of venom. In addition to their harmful effects, these actions delay the

transport of patients to health centers and, therefore, jeopardize the adequate management of these cases. First aid interventions should be focused on the immobilization of the bitten extremity and the rapid transportation to clinics or other health facilities. Communities should have strategies for rapid deployment of snakebitten people to medical treatment; an example is the use of motorcycle transportation in Nepal (Alirol et al., 2010). The interaction and communication of health staff with local healers is very important, in order to promote partnerships aimed at reducing harmful interventions and guaranteeing rapid mobilization for antivenom administration. The application of pressure-immobilization, by applying a bandage and a splint to the entire bitten limb, has been used in Australia for delaying the systemic absorption of neurotoxic venoms (Sutherland et al., 1979; White, 2010). Recently, a pharmacological intervention, based on the application of an ointment containing a nitric oxide donor, aimed at reducing the lymphatic absorption of venom, has been proposed (Saul et al., 2011), and its testing in the clinical setting is pending.

6.3 Antivenoms: The key therapy of snakebite envenoming

The parenteral administration of animal-derived antivenoms constitutes the mainstay in the therapy of snakebite envenoming (WHO, 2007a, 2010a), since the development of the first antivenoms, the *serum anti-venimeux*, during the last decade of the XIXth century (Bon, 1996). Antivenoms are preparations of immunoglobulins, or immunoglobulin fragments $F(ab')_2$ or Fab, obtained by fractionating the plasma of animals immunized with snake venoms (Gutiérrez et al., 2011a; Lalloo & Theakston, 2003; WHO, 2010a). Antivenoms can be monospecific, when animals receive the venom of a single species, or polyspecific, when venoms from two or more species are injected. The majority of manufacturers use horses for immunization, although few use sheep and donkeys (Gutiérrez et al., 2011a, 2011b). In most cases, plasma fractionation involves the digestion of proteins with pepsin or, by few producers, with papain, followed by the purification of antibody fragments by salting-out with ammonium salts or caprylic acid fractionation and, in some cases, with chromatographic procedures (dos Santos et al., 1989; Grandgeorge et al., 1996; Raw et al., 1991; WHO, 2010a). Some producers fractionate plasma with caprylic acid to obtain whole IgG preparations (Gutiérrez et al., 2005; Rojas et al., 1994). A detailed description of the methods used in animal immunization and plasma fractionation for antivenom production can be found in the *WHO Guidelines for the Production, Control and Regulation of Snake Antivenom Immunoglobulins* (WHO, 2010a). There are antivenom-manufacturing laboratories in every continent (a complete list can be found in http://apps.who.int/bloodproducts/snakeantivenoms/database/). Following manufacture, antivenoms are subjected to a quality control protocol which involves physical, chemical and biological tests aimed at ensuring the efficacy and safety of these products (Gutiérrez & León, 2009; WHO, 2010a).

The ability of antivenoms to neutralize venom toxins is based on the capacity of antivenom antibodies, or antibody fragments, to bind and neutralize the most relevant toxins in a venom. It has been proposed that such neutralization is based on, at least, four mechanisms: (a) Binding of antibody paratopes to epitopes located at the pharmacologically-relevant molecular region, i.e. the catalytic active site in toxic enzymes such as phospholipases A_2 and metalloproteinases. (b) Binding of antibodies to epitopes located close to the toxin active site, thus exerting inhibition by steric hindrance. (c) Binding of antibodies to molecular regions distant from the active/toxic site of venom components, neutralization being achieved by allosteric changes induced in the toxins, with the consequent reduction in their

ability to bind to tissue or cellular targets and to cause damage. (d) Formation of immunocomplexes between antibodies and toxins, with the subsequent removal by phagocytic cells; this last mechanism does not operate in the case of antivenoms made of monovalent Fab fragments, since they do not form complexes (Gutiérrez & León, 2009; Gutiérrez et al., 2011b).

6.3.1 Clinical performance of antivenoms: Efficacy

Antivenoms are administered parenterally, mostly by the intravenous route, and preferably diluted in physiological solution. Intradermal hypersentivity tests are not recommended since they have a very poor predictive value (Cupo et al., 1991; Malasit et al., 1986). The clinical performance of antivenoms depends on several factors associated with the immunological and physico-chemical characteristics of these products, as well as with the circumstances of their use in the clinical setting. At the preclinical level, antivenoms should be effective in the neutralization of the most relevant toxic activities of the venoms of medically-relevant snakes in a particular country or region. In some cases, this is achieved by using antivenoms raised against the venoms of the species that provoke the bite. In other cases, antivenoms are able to neutralize the venoms of species not used in the immunization of animals, but being phylogenetically related (WHO, 2010a). This phenomenon of immunological cross-reactivity has been clearly demonstrated, for instance, in the case of antivenoms raised against *Bothrops* sp venoms in Latin America (Otero et al., 1995; Segura et al., 2010a). In other cases, however, the cross-reactivity of antivenoms is low and, therefore, the efficacy of some products to neutralize venoms of medically-relevant species not included in immunization mixtures is limited, as occurs with venoms of some rattlesnakes and coral snakes in the Americas (Saravia et al., 2002; Tanaka et al., 2010). This issue of low cross-reactivity of some antivenoms may have potentially serious implications, when some products are used in the treatment of envenomings by species whose venoms are immunologically different from the ones used in immunization. One example has been the use of antivenoms manufactured in India for the treatment of envenomings in sub-Saharan Africa (Visser et al., 2008). This problem is complicated by the frequent lack of regulation and quality control of imported antivenoms in many countries, thus precluding the proper assessment of their neutralizing ability. This issue urges upgrading the regulatory capacities of countries in Asia, Africa and Latin America, as to ensure that antivenoms being introduced in these regions are evaluated with standard preclinical tests, such as those recommended by the WHO (2010a).

Antivenoms have demonstrated to be highly effective, when administered timely, at halting the most relevant systemic manifestations of snakebite envenoming (Gutiérrez & León, 2009; Lalloo & Theakston, 2003; Warrell, 1992). In the case of bites by viperids, systemic bleeding, hemodynamic manifestations and coagulation disturbances are controlled within hours after antivenom infusion. In contrast, toxins responsible for local pathological effects (edema, dermonecrosis, local hemorrhage and myonecrosis) are more difficult to neutralize by antivenoms, basically because the early onset of these effects upon venom injection, thus precluding an effective blockade by antivenom antibodies (Gutiérrez et al., 1998), a problem that is worsened by the occurrence of venom-induced vascular alterations, which affect the distribution of antivenom to the affected tissue (Battellino et al., 2003). In the case of neurotoxic venoms, characteristic of most elapid and some viperid species, the development of neurotoxic manifestations is prevented by the timely administration of antivenoms, with

the consequent neutralization of neurotoxins in the circulation before reaching neuromuscular junctions. However, neutralization is more difficult when neurotoxins are bound to receptors at the synapse. In the case of post-synaptic neurotoxins, their binding can be reverted (Alape-Girón et al., 1996; Boulain & Ménez, 1982), but presynaptically-acting toxins are known to destroy the nerve terminal, thus precluding neutralization and generating a more prolonged pattern of nerve damage (Prasarnpun et al., 2005). Thus, the clinical efficacy of antivenoms is intimately related to the ability of these products to bind with high affinity and neutralize relevant venom toxins located in tissues or in the bloodstream, as well as to the toxicokinetics of toxins and the pharmacokinetics of antivenom antibodies or antibody fragments (Gutiérrez et al., 2003; Scherrmann, 1994; WHO, 2010a). For instance, low molecular mass neurotoxins characteristic of elapid snake venoms are rapidly distributed and readily reach their targets in the neuromuscular junctions; in these cases, there is a mismatch between the toxicokinetics of these neurotoxins and the pharmacokinetics of antivenom antibodies (Gutiérrez et al., 2003; Ismail et al., 1998). On the other hand, low molecular mass Fab fragments have a relatively short half-life, thus resulting in the phenomenon of recurrence of envenoming, i.e. the reappearance of signs and symptoms of envenoming several hours after antivenom therapy (Ariaratnam et al., 1999; Boyer et al., 2001; Meyer et al., 1997). Careful clinical following up of patients is necessary to determine the need of an additional dose of antivenom.

The rapid access to effective antivenoms constitutes a key issue in the proper management of snakebite envenoming. If the envenoming is potentially severe, and if the access to antivenom is delayed, due to reasons that range from hesitation to use antivenoms to prolonged transportation times to health facilities and lack of antivenoms in health posts, the efficacy of antivenoms is jeopardized and various pathophysiological complications might ensue. Another factor that determines the efficacy of antivenom treatment has to do with the use of a correct dose of this immunobiological, and to the assessment of whether the patient needs an additional dose of antivenom, based on the evolution of clinical and laboratory parameters. These considerations demand that the health staff in charge of treating these envenomings have an adequate knowledge of the basic elements of antivenom usage.

6.3.2 Antivenom safety

Administration of antivenom is associated, in a variable percentage of cases, with early and late adverse reactions. Early adverse reactions (EARs) can be, in few cases, truly anaphylactic reactions, i.e. IgE-mediated, or, alternatively, anaphylactoid reactions, which occur more frequently, and are *de novo* reactions not mediated by previous exposure to horse proteins (Warrell, 1995a). The mechanisms of these reactions are not well understood, but are likely to depend on (a) complement activation by antibody aggregates present in antivenom (Sutherland, 1977); (b) formation of complexes between human heterophylic antibodies against antivenom antibodies, with consequent complement activation (León et al., 2008); or (c) presence of antibodies in antivenoms that react with cells, such as erythrocytes (León et al., 2007), leukocytes or endothelial cells, thus provoking adverse reactions. Such EARs can be mild, characterized by urticaria and itching only, or severe, involving angioedema, bronchospasm and hypotension (Warrell, 1995a). The incidence of EARs varies significantly among different antivenoms, from as low as 5% to higher than 70% of the cases with some products (Chippaux et al., 1998; Gawarammana et al., 2004;

Otero-Patiño et al., 1998). Such high variability is due to the different physicochemical quality of antivenoms, since some products have high protein concentration and high amounts of protein aggregates. Therefore, the physicochemical features of antivenoms greatly determine their safety profile, an issue that demands renewed efforts at the technological and regulatory levels. Another type of reaction observed in some antivenoms are pyrogenic reactions, associated with chills and fever (WHO, 2010b), but these should be avoided by a proper quality control, i.e. pyrogenicity testing, of these products. In the event of EARs, antivenom infusion should be stopped, and the reaction treated with adrenaline, anti-histamines and steroids (Warrell, 1995a). Once the reaction is controlled, antivenom infusion should be continued. Pretreatment with adrenaline has been advocated for reducing the incidence of EARs (de Silva et al., 2011). Late adverse reactions (LARs) to antivenoms occur 5-24 days after treatment, and are characterized by itching, fever, urticaria, arthralgia and proteinuria (Warrell, 1995a). This corresponds to a typical type III hypersensitivity reaction, i.e. serum sickness, due to the formation of immune complexes between antivenom antibodies and antibodies generated in the patient against antivenom proteins. The incidence of serum sickness after antivenom administration correlates with the amount of foreign protein, i.e. antivenom, administered (LoVecchio et al., 2003). LARs are treated with anti-histamines and steroids. Another aspect of antivenom safety that has to be considered is microbial safety, which is guaranteed by sterile filtration of the final product and the use of viral inactivation/removal steps (Burnouf et al., 2004; WHO, 2010a). Some of the manufacturing steps currently used in antivenom production inactivate or remove viruses, thus contributing to the microbial safety of these products (Burnouf et al., 2004; WHO, 2010a).

Such high heterogeneity in the safety of antivenoms, in terms of incidence of adverse reactions, calls for international cooperative efforts aimed at improving the technological platform of many antivenom producers, in order to increase the physicochemical quality of antivenoms on a world wide basis (Gutiérrez et al., 2011a). A number of antivenom producers in Asia, Africa and Latin America need to upgrade their facilities and protocols. The experience gained by well-developed antivenom manufacturing laboratories in various parts of the world should contribute to the improvement of less developed antivenom producers, through a variety of activities such as technology transfer programs, workshops, training and exchanges of various sorts. Such networking scenario should be promoted by the WHO and its regional offices, and by organizations such as the Global Snake Bite Initiative (www.snakebiteinitiative.org/).

6.4 Ancillary treatments

The therapy of snakebite envenoming includes a series of interventions in addition to antivenom administration. In the case of viperid venoms, hemodynamic and renal disturbances demand careful control of fluid therapy, monitoring of central venous pressure, and use of diuretics (Warrell, 1995a; WHO, 2010b). Infection often develops in viperid snakebites and requires the use of antibiotics. Moreover, local tissue damage by viperid and some elapid snakebites calls for debridement of necrotic tissue and care of the bitten limb. In some cases, when muscle intracompartmental pressures increase beyond 45 mm Hg, compartment syndrome ensues and fasciotomy is indicated (WHO, 2010b). In the case of neurotoxic envenomings caused by elapid and some viperid species, mechanical ventilation should be provided in the event of respiratory paralysis (Warrell, 1995a; WHO,

2010b). The complexity of snake venoms and the corresponding variability in the clinical presentation of these envenomings complicates the management of the cases and demands an adequate training of the health staff in charge of treating these emergencies, in order to guarantee the implementation of effective therapeutic interventions.

The poor efficacy of antivenoms to neutralize local tissue damage induced by viperid and some elapid venoms brings the need to find alternative therapies. A very promising avenue is the possibility of using natural or synthetic inhibitors of venom toxins, such as inhibitors of phospholipases A_2, metalloproteinases and hyaluronidases, for blocking the action of tissue-damaging toxins by rapidly administering these inhibitors directly on the site of venom injection (Gutiérrez et al., 2007; Lomonte et al., 2009; Perales et al., 2005). Such possibility has been tested, with excellent results, at the preclinical level in mouse models (Borkow et al., 1997; Lomonte et al., 2009; Rucavado et al., 2000; Yingprasertchai et al., 2003). It is necessary to identify and develop inhibitors, some of which may be already in use for other pathologies, and to test them at the preclinical and clinical levels. The therapy of snakebite envenoming in the future will likely involve, in addition to intravenous antivenom administration, the local injection of toxin inhibitors, as well as other ancillary interventions aimed at controlling the systemic aspects of envenoming and to modulate the deleterious aspects of the inflammatory response of the organism to snake venoms (Gutiérrez et al., 2007).

7. Preclinical and clinical testing of antivenoms

The large intra- and interspecies variability in the composition of snake venoms poses a problem for antivenom efficacy, since cross-neutralization of antivenoms against venoms not used in the immunizing mixture might not occur. Therefore, the distribution of antivenoms to countries or regions where medically-relevant snakes are different from those used in immunization schemes needs to be carefully evaluated in order to ensure that these antivenoms are indeed effective. This issue gets complicated by the fact that, quite often, regulatory agencies in developing countries do not have the facilities and expertise to perform adequate preclinical testing of the antivenoms being imported (D. Williams et al., 2011). A proper assessment of antivenom efficacy should be based on preclinical and clinical testing. At the preclinical level, it is necessary to assess the capacity of antivenoms to neutralize the lethal, as well as other relevant toxic activities, of the most important venoms in a country or region. This demands, in the first place, the establishment of local facilities to collect and keep medically-relevant snakes. These snake colonies should provide pools of venoms, which could then be used in preclinical testing of antivenoms. Precise indications on how to built and run these facilities are included in the *WHO Guidelines for Antivenom Production, Control and Regulation of Antivenoms* (WHO, 2010a). In the case of viperid venoms, a battery of preclinical tests usually includes the evaluation of the neutralization of lethal, hemorrhagic, coagulant, defibrinogenating and myotoxic activities (Gutiérrez et al., 2011b; Theakston, 1986; WHO, 2010a). In the case of elapid snakes, antivenom preclinical efficacy should be assessed by the neutralization of lethality and, in the case of elapid venoms that induce necrosis or coagulopathy, by the neutralization of dermonecrosis and coagulant activities, respectively (Gutiérrez et al., 2011b; WHO, 2010a). These methods involve simple laboratory procedures that need to be implemented in countries where antivenoms are being produced or imported. In addition, international collaborative

projects, involving well-developed laboratories, could be implemented in order to test antivenoms (D. Williams et al., 2011). More recently, a proteomic approach, named 'antivenomics', has been adapted for the evaluation of immune reactivity of antivenoms against particular toxins in venoms (Calvete, 2010; Gutiérrez et al., 2009a; Lomonte et al., 2008). This methodology allows for the identification of the toxins recognized by antivenom antibodies.

The preclinical assessment of antivenoms should be followed by clinical evaluation of antivenom safety and efficacy (WHO, 2010a). Since phase I clinical trials in healthy volunteers are ethically unacceptable in the case of antivenoms, because they might induce adverse reactions, a substitution of phase I clinical trial, by a protocol known as '3 + 3 dose escalation design', has been proposed for antivenoms (S.B. Abubakar et al., 2010b). This is then followed by phase III clinical trials in which a new antivenom is compared with an existing antivenom of known efficacy and safety (see for example the studies of I.S. Abubakar et al., 2010; Cardoso et al., 1993; Otero et al., 1999; Otero-Patiño et al., 1998; Smalligan et al., 2004; Warrell et al., 1974). Clinical trials should use robust clinical and laboratory end points for the assessment of therapeutic success. Furthermore, post-marketing surveillance (pharmacovigilance) is required to detect possible adverse reactions not reported in the clinical trials and to follow up efficacy (WHO, 2010a).

8. Technological aspects for antivenom improvement

The need to have antivenoms of wide cross-reactivity, able to neutralize venoms from as many snake species as possible, demands a careful revision of the design of venom mixtures used for immunization of animals. There is a large body of knowledge in the biochemistry, toxicology and immunology of snake venoms, especially of venoms from species having a heavy medical impact, which should be used for the re-evaluation of the immunizing mixtures and for the design of novel mixtures for new antivenoms (Gutiérrez et al., 2009a; D. Williams et al., 2011). Proteomics technologies, together with neutralization tests, constitute valuable tools to analyze venom composition and effects, and to assess the neutralizing profile of current and new antivenoms. The Global Snake Bite Initiative has proposed a strategy to structure an international collaborative effort to evaluate current antivenoms and to design improved antivenoms (D. Williams et al., 2011). One aspect of this strategy is based on the development of regional polyspecific antivenoms for use in sub-Saharan Africa and Asia using clinical, phylogenetic, proteomic and antivenomic analyses for the selection of the best venom mixtures for immunization. These antivenoms, manufactured by several laboratories, will then be evaluated by independent preclinical assessment, followed by clinical trials in various countries, performed by local medical personnel. In parallel, international expert committees will validate production facilities for prequalification, in a process aimed at ensuring the manufacture of the volume of antivenom needed in those regions (D. Williams et al., 2011).

One example of the potential usefulness of such an approach has to do with the design of immunizing mixtures for antivenoms to be used in sub-Saharan Africa. Several antivenoms use a mixture of venoms from many species; however, a recently developed antivenom was produced by using a mixture of venoms from only three species (Gutiérrez et al., 2005). Neutralization and antivenomic studies have shown that this new antivenom is able to

neutralize the venoms of several species of viperids and spitting cobras from sub-Saharan Africa (Calvete et al., 2010b; Segura et al., 2010b; Petras et al., 2011). Similarly, the ideal venom mixtures for antivenoms to be used in some parts of Asia need to be re-assessed on the basis of recent clinical evidence of the existence of medically-relevant species whose venoms are not routinely used in antivenom manufacture, such as that of the viperid *Hypnale hypnale* (Ariaratnam et al., 2008). Likewise, the decision on whether to prepare monospecific or polyspecific antivenoms has to be based on sound epidemiological, clinical, biochemical and immunological evidence. Consequently, the design and re-design of venom mixtures for immunization requires a multidisciplinary approach. On the other hand, there are other aspects of antivenom technological development that should be considered, such as stability and improved immunization schemes. Liquid antivenoms have to be stored at 2-8 ^{o}C (WHO, 2010a). However, the quality of the cold chain in many regions of the world is poor, thus complicating the distribution of antivenoms, especially to rural settings where most snakebites occur. This problem can be overcome by producing freeze-dried antivenoms, but this increases the production cost and, therefore, the price. Alternatives are being explored aimed at formulating liquid antivenoms stable at room temperature (Rodrigues-Silva et al., 1999; Segura et al., 2009). Likewise, the design of immunization protocols based on multi-site injection of small volumes containing low amounts of venom has resulted in higher neutralizing titers with very little damage to the immunized animals (Chotwiwatthanakun et al., 2001). Furthermore, the search for novel adjuvants is a relevant task in the efforts to improve antivenom antibody titers (Gutiérrez et al., 2011a).

9. The accessibility and correct use of antivenoms

Despite the widespread demonstration of antivenom efficacy for the treatment of snakebite envenoming, and the fact that many aspects of the know-how required to produce antivenoms are freely available (WHO, 2010a), there is a current deficit in antivenom accessibility in various regions of the world, most notably in sub-Saharan Africa and some countries of south-east Asia (Chippaux, 2010; Theakston et al., 2003; D. Williams et al., 2011; WHO, 2007a). This phenomenon has multiple causes, such as: (a) Withdrawal of some manufacturers from these markets due to profit considerations. (b) Privatization of former public laboratories, with the consequent increments in the prices of antivenoms. (c) The impact of international policies designed to reduce the size of the public sector, including a reduction in the provision of public health services and their privatization. (d) Weakening of antivenom manufacturing laboratories of the public sector in many developing countries, associated with lack of investment in facilities and technology, and reduction in training programs for the staff. (e) Lack of financial support for antivenom purchase by ministries of health, due to economic constraints and to prioritization on other health issues perceived as more pressing needs. (f) Loss of confidence in antivenom treatment in some regions due to the use of antivenoms of poor efficacy or safety. (g) Poor advocacy for promoting greater attention to snakebite envenoming as a neglected tropical disease. (h) Low profile of snakebite envenoming in the international public health agenda. As a result, antivenom accessibility is deficient in vast regions of Asia and Africa (WHO, 2007a; D. Williams et al., 2011). The solution to this complex problem demands concerted actions at various levels, from the technological and manufacturing realm to the public health arena (Chippaux, 2010; Gutiérrez et al., 2010b; D. Williams et al., 2010, 2011).

9.1 How to enhance the accessibility of antivenoms

Economic and political constraints constitute one of the main causes of poor accessibility of antivenoms in many countries. It is evident that the sole drive of the market forces will not solve this problem and, instead, well-designed strategies with a strong participation of governments and non-governmental organizations have to be implemented. This is a critical aspect that needs to be addressed by a variety of interventions such as: (a) Increasing the technological capacity of manufacturing laboratories in developing countries, both in the public and private realms, and introduction of cost-effective methodologies for antivenom production. One example is the manufacture of whole IgG antivenoms by caprylic acid fractionation of plasma (Gutiérrez et al., 2005; Rojas et al., 1994). This procedure generates antivenoms of high quality and high yield, at reduced production costs, thus constituting an excellent alternative for low-income countries (Brown & Landon, 2010). (b) Increased recognition of governments of low-income countries on the impact of snakebite envenoming as a public health problem, with the consequent political and financial decisions for the acquisition of adequate volumes of antivenom. (c) Using the capacity of large antivenom producers in order to manufacture antivenoms for other regions of the world at reasonable prices. This could be accomplished by promoting international partnerships between manufacturers, public health authorities, organizations of the civil society, and donors, similarly to what has been done for other neglected tropical diseases (Hotez et al., 2006). (d) Promoting strategies for price reduction, such as differential pricing arrangements or large scale 'pooled' purchases for various countries (Gutiérrez et al., 2010b).

9.2 Distribution of antivenoms: guaranteeing access to regions where snakebites occur

Even if governments purchase adequate volumes of antivenom, this does not guarantee that these drugs will reach the rural health posts where most snakebite envenomings occur. This problem has diverse roots, such as: (a) Incomplete information on the epidemiology of snakebites. In countries where official statistics of snakebite incidence are lacking or incomplete, the decision on where to distribute antivenoms cannot be taken on a rigorous base. This is another reason for underscoring the relevance of proper epidemiological register of this pathology. (b) Antivenom acquisition procedures by the ministries of health in many countries are slow and cumbersome; moreover, due to budgetary constraints, the volumes of antivenom purchased are often insufficient; both of these factors preclude the distribution of adequate volumes of this drug to rural settings. (c) Antivenoms are often distributed only to hospitals and clinics in large cities, distant from the regions where the majority of snakebites occur, thus affecting the timely treatment of patients. (d) As discussed previously, the lack of an adequate cold chain system in many rural settings of the world precludes the effective distribution of antivenoms. (e) Many rural regions are devoid of healthcare facilities, thus affecting the access to antivenom and other medical interventions and forcing people to travel large distances to receive medical attention.

This complex scenario demands the design of well-structured and effective strategies of antivenom distribution, on the basis of sound epidemiological information on snakebite incidence. An intersectorial and interprogrammatic approach should be promoted, in conjunction with other efforts being performed in the public health realm, in order to favour a synergy with other actors and projects, with the consequent impact in the cost-

effectiveness of interventions (WHO, 2007c). The compulsory report of snakebite envenoming (WHO, 2010a) and the use of geographical information systems to identify high risk areas (Hansson et al., 2010; Leynaud & Reati, 2009) would greatly contribute to generate a solid basis of information on the actual magnitude of the problem. Furthermore, the awareness of national and regional health authorities on the impact of snakebite envenoming should be promoted by academic, public health and civil society organizations, in order to ensure the acquisition and distribution of the required volumes of antivenom. Likewise, antivenom distribution strategies should benefit from the use of the cold chain system already developed for vaccine distribution. Also, the provision of antivenom access to rural settings and the training of rural health staff in the correct administration of antivenoms should be prioritized. Interventions tailored to the conditions of each country and region should be promoted, in order to optimize the available resources and guarantee a rapid access to treatment (see for example Otero et al., 1992).

9.3 Promoting the correct use of antivenoms

The distribution of antivenoms to regions where snakebites occur should be complemented by a proper training of health staff in the correct usage of this product and in the proper treatment of snakebite envenomings. There is evidence of poor knowledge of medical and nursing staff in various regions of the world on how to diagnose and treat snakebite envenomings, how to use antivenoms, and how to treat possible adverse reactions to their administration (Gutiérrez et al., 2009c; Simpson, 2008). This requires concerted efforts at medical and nursing schools in the universities, as well as the implementation of permanent educational programs on this subject, particularly aimed at rural health facilities. Likewise, the implementation of teaching material and the development of guidelines for the diagnosis and treatment of snakebite envenomings should be actively promoted, both at regional (WHO, 2010b) and national levels. These tasks should involve not only teaching institutions, but also public health authorities, local organizations of the civil society, and antivenom manufacturers. The critical revision of antivenom prospects, on the basis of current knowledge on the taxonomy of snakes and on the clinics of snakebite envenomings, are of great relevance, in the light of evident misconceptions included in the prospects of some antivenoms (Simpson & Norris, 2007).

10. Prevention of snakebites

Prevention programs aimed at reducing the impact and incidence of snakebite envenomings should be a priority in the international efforts required to confront this problem. The design of these programs should be tailored to the cultural, social, economic and institutional characteristics of the populations, and should involve the active participation of the communities in their design and implementation. Impoverished and excluded groups, such as indigenous communities in many parts of the world, should receive particular attention. The design of these programs should be also based on sound social science research aimed at understanding the particularities and needs of each region and context, with the participation of the communities. It is highly relevant, for instance, to understand how the problem is perceived in the community and what types of preventive interventions are suited for each particular context. Likewise, specific strategies should be designed for situations involving natural disasters, as snakebites have been reported to increase in such

circumstances. In addition, the natural history of envenomings should be considered, including the distribution of snakes in various types of crops and the behaviour of snakes. In some regions of Asia, bites by kraits (genus *Bungarus*) often occur at nights inside human dwellings while people are asleep on the ground (Sharma et al., 2004). The use of mosquito nets has reduced the incidence of envenoming by kraits in Nepal (Chapuis et al., 2007). The majority of viperid snakebites occur in the feet; thus, a preventive measure should be the use of footware (Alirol et al., 2010; Gutiérrez, 2010; Warrell, 2010).

11. Final remarks: The need for an integrated approach and for the promotion of partnerships

The world wide efforts required to reduce the impact of snakebite envenoming should be conceptualized within the frame of the Millennium Development Goals (MDGs) (http://www.un.org/millenniumgoals/global.shtml), particularly regarding the provision of access to essential drugs (WHO, 2011), in this case antivenoms, to developing countries. The access to adequate health services is a human right, and states and other international instances have the obligation to ensure the access to health facilities, goods and services on a non-discriminatory basis, especially to vulnerable and marginalized groups, and to provide education and access to information to the communities on relevant health issues, such as snakebite envenoming. Therefore, interventions aimed at ameliorating the impact of this pathology should be viewed within a frame of human rights and social responsibility of states, international organizations and non-governmental groups.

Snakebite envenoming is a 'tool-ready' disease, in the sense that the basic technological therapeutic tools to treat this pathology, i.e. antivenoms, are available. However, there is a need to implement renewed efforts to improve the quality of some antivenoms, to design new antivenoms for various regions in the world, and to increase the volume of production as to fulfil the world wide needs to these immunobiologicals. Scientific, technological and public health tasks include acquisition of more rigorous data on the incidence of snakebite incidence and mortality, assessment of preclinical and clinical performance of currently available antivenoms, and development of novel antivenoms on the basis of epidemiological, biochemical, toxicological and immunological knowledge on venoms. Moreover, the strengthening of antivenom manufacture on a global basis should involve an active process of technology transfer and training aimed at improving the current technological platform of many antivenom producers, especially those located in developing countries. Finally, renewed efforts should be undertaken to guarantee the deployment and effective distribution and use of antivenoms to the regions of the world where this pathology has its highest impact. Table 1 summarizes some of the most pressing tasks that need to be promoted as part of a global strategy to reduce the impact of snakebite envenomings.

The design of effective strategies to confront this problem should be also integrated with the more general efforts in the arena of neglected tropical diseases (WHO, 2007c). Such strategies should be conceived from an intersectorial and interprogrammatic perspective (see WHO, 2007c), with a synergistic approach involving the control of other neglected tropical diseases; such an approach will significantly increase the cost-effectiveness of interventions. Areas of possible interprogrammatic cooperation include: (a) The collaborative delivery of antivenoms

within distribution channels already developed for other immunobiologicals, such as vaccines. (b) Incorporating antivenoms in integrated drug purchasing schemes in developing countries on a regional basis. (c) Strengthening the development of public health systems in remote rural areas where snakebite envenomings are frequent. (d) Promoting partnerships of diverse sorts with groups involved in the combat of neglected tropical diseases, such as foundations, non-governmental organizations and other advocacy groups. (e) Including snakebite envenoming in the agenda of organizations that provide financial support for research and intervention programs for neglected tropical diseases in developing countries. (f) Incorporating the subject of snakebite prevention, diagnosis and treatment within the context of educational packages on neglected tropical diseases in teaching institutions, public health facilities and communities. (g) Promoting the inclusion of the subject of snakebite envenoming within the agenda of community organizations for the promotion of health in rural areas of countries in Africa, Asia and Latin America.

1. Acquisition of reliable information on snakebite incidence and mortality
2. Innovation in the technology for the production of antivenoms
3. Strengthening the capacity of laboratories in low-income countries to manufacture and control antivenoms
4. Commitment of manufacturers to produce antivenoms for regions devoid of local production
5. Implementation of economic strategies to ensure the sustainable production of antivenoms
6. Improvement of the national regulatory expertise and quality control of antivenoms in low-income countries
7. Accessibility of antivenoms at affordable prices in low-income countries
8. Preclinical and clinical assessment of antivenom efficacy and safety
9. Development of effective antivenom distribution programs to regions of high incidence of snakebites
10. Permanent training programs for health staff on snakebite envenomings and their treatment
11. Development of programs to support people suffering from sequelae of snakebite envenomings
12. Preventive and educational programs at the community level with involvement of local organizations

Table 1. Summary of some of the most important tasks for an integrated strategy to confront the problem of snakebite envenoming from a global perspective. Adapted from Gutiérrez et al. (2010b)

In the long term, the reduction of the impact of snakebite morbidity and mortality, with its drastic effects on the quality of human life, should involve a global partnership incorporating many different actors at various levels in our societies, such as: (a) The scientific ('epistemic') community of toxinologists, represented by the International Society on Toxinology (IST) and researchers in every continent. (b) Groups working on technological development and technology transfer activities, both in the pharmaceutical industry and in university departments. (c) Antivenom manufacturers. (d) International health organizations, especially the WHO and its regional offices. (e) National public health

authorities, i.e. Ministries of Health and other organizations of the public health sector. (f) National regulatory bodies, responsible for ensuring the safety and efficacy of antivenoms being distributed. (g) Non-governmental organizations (NGOs) and advocacy groups that promote a public health agenda and the access of essential drugs to developing countries. (h) Organizations of the civil society of countries having a high burden of snakebite envenoming (Figure 2). The current tasks of generating a growing international awareness on the magnitude of this problem, establishing partnerships to ensure the development, availability and accessibility to antivenoms, and promoting prevention and an effective clinical management of this pathology, are being promoted by the Global Snake Bite Initiative (GSI), the WHO, and a number of national and regional projects in various parts of the world.

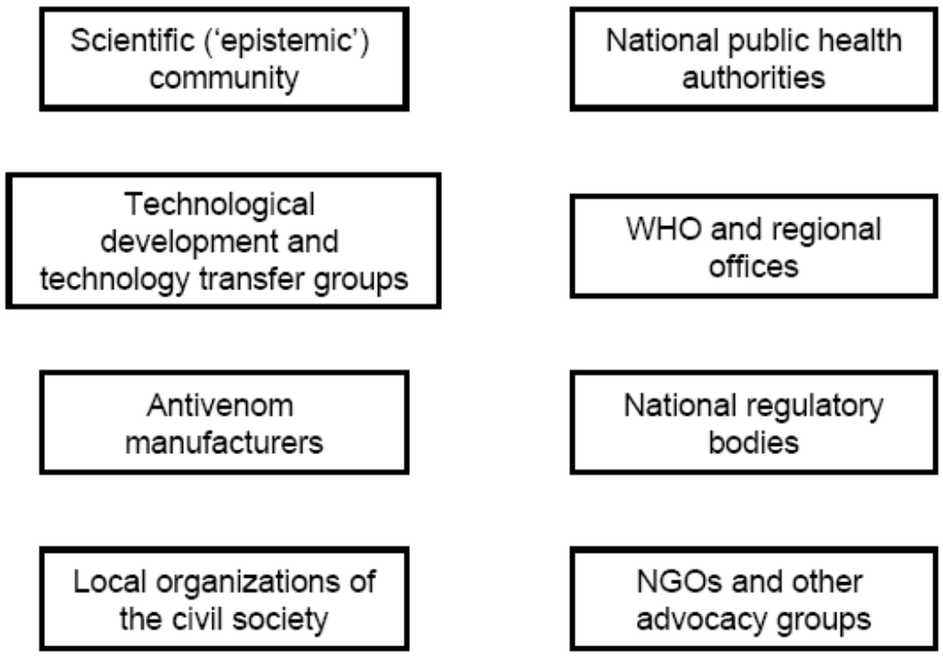

Fig. 2. Some of the participants that should be involved in a global partnership aimed at the reduction of the impact of snakebite envenoming in the world.

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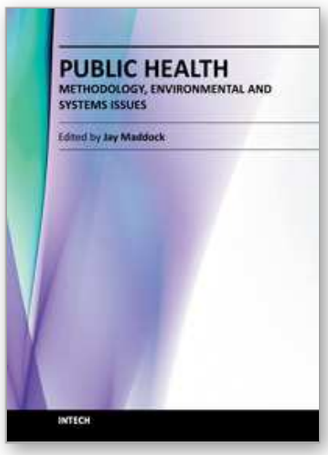

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Public health can be thought of as a series of complex systems. Many things that individual living in high income countries take for granted like the control of infectious disease, clean, potable water, low infant mortality rates require a high functioning systems comprised of numerous actors, locations and interactions to work. Many people only notice public health when that system fails. This book explores several systems in public health including aspects of the food system, health care system and emerging issues including waste minimization in nanosilver. Several chapters address global health concerns including non-communicable disease prevention, poverty and health-longevity medicine. The book also presents several novel methodologies for better modeling and assessment of essential public health issues.

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